REMARKS

Entry of the amendments presented above is respectfully requested. Upon entry of these amendments, claims 1-2, 4-5 and 7-41 will be pending in the Continuation Application.

Support for some of the amendments made to claim 1 is present in the application at page 3, lines 5-6, and in the originally-filed claims.

Provisos have been added to claim 1 and to new claim 37 of the Continuation Application, which have the effect of excluding phenyl, and methoxybenzyl and methyl, respectively, from the definition of the R variable. Applicants submit that these provisos do not constitute new matter because the provisos have the effect of narrowing, not broadening, the invention that is claimed in these claims (excluding compounds that were encompassed within Applicants' originally-filed claims). See In re Johnson and Farnham, 194 USPQ 187 (CCPA 1977) and In re Driscoll, 195 USPQ 434 (CCPA 1977).

In In re Johnson and Farnham, provisos were added by the patent applicant to the originally-filed claims in order to exclude two species of chemical compounds that were originally encompassed within the originally-filed claims, and one of which was lost during an interference proceeding. In this case, like with amended claim 1 and new claim 37 of the Continuation Application, the effect of the provisos was that the patent applicant was claiming less than the full scope of his disclosure. The CCPA made the following statements in this case concerning the addition of provisos to claims:

> "Inventions are constantly made which turn out not to be patentable, and applicants frequently discover during the course of prosecution that only a part of what they invented and originally claimed is patentable...
>
> To deny appellants the benefit of their grandparent application in this case would, as this court said in Saunders, let form triumph over substance, substantially eliminating the right of an applicant to retreat to an otherwise patentable species merely because he erroneously thought he was first with the genus when he filed...
>
> The notion that one who fully discloses, and teaches those skilled in the art how to make and use, a genus and numerous species therewithin, has somehow failed to disclose, and teach those skilled in the art how to make and use, that genus minus two of those species, and has thus failed to satisfy the requirements of §112, first paragraph, appears to result from a hypertechnical application of legalistic prose relating to that provision of the statute. All that happened here is

> that appellants narrowed their claims to avoid having them read on a lost interference count...
>
> Here, as we hold on the facts of this case, the 'written description' in the 1963 specification supported the claims in the absence of the limitation, having described the whole necessarily described the part remaining." [Emphasis added.]

Like the facts in In re Johnson and Farnham, Applicants originally-filed specification contains a broad and complete generic disclosure, coupled with examples that are fully supportive of the invention claimed in amended claim 1 and in new claim 37, and Applicants have narrowed, rather than broadened, claim 1 and new claim 37, with the full scope of the claimed invention being supported by the originally-filed specification, generically and by examples.

If the examiner takes the position that the provisos that have been added to claims 1 and 37 of the application constitute new matter, Applicants respectfully request that the examiner provide for Applicants the citations to the case (or other) law that is used to support the examiner's position.

1. Rejection of Claims 1, 4, 7-9 and 10 under 35 U.S.C. §103(a)

In an office action for parent application Serial No. 09/840,768 having a mailing date of September 9, 2002 (hereinafter "the office action"), the Examiner rejected claims 1, 4, 7-9 and 10 of the application under 35 U.S.C. §103(a) as being unpatentable over Johns et al., Journal of Ethnopharmacology 5, 149-161, 1982 ("Johns et al.").

In the office action (page 3), the Examiner stated that Applicants claim a compound of the formula given in claim 1 of the present application. Referring Applicants to compound (V) on page 152, and the last five lines of the third paragraph on page 156, of Johns et al., the Examiner stated that, "Johns et al. teach an isomer of the compound(s), named N,N-di(methoxy-4-benzyl) thiourea, defined by the claims of the present application." The Examiner stated that the difference between the Applicants' claimed invention and what is taught in the Johns et al. reference is that the reference's thiourea compound is the positional isomer to that of the presently claimed compound(s). The Examiner stated that the methoxy substituent on the benzene ring is in the para position, whereas in the presently claimed compound(s) the methoxy substituent is in the

meta position. The Examiner stated that it is common knowledge to those skilled in the art that isomers possess similar chemical and physical properties. Thus, the Examiner stated that it would have been prima facie obvious to one of ordinary skill in the art, in view of the Johns et al. reference, to arrive at the presently claimed thiourea compound(s) of the presently claimed formula because Johns et al. teach an isomer of the presently claimed compound(s). The Examiner further stated that one of ordinary skill in the art would have been motivated, in view of the teachings present in the Johns et al. reference, to obtain meta- or ortho-isomeric compounds of formula (V), which is taught by Johns et al., so as to use them as estradiol inhibiting agents. The Examiner stated that the instantly claimed compounds would therefore have been obvious to one of ordinary skill in the art.

For the reasons presented below, Applicants respectfully traverse the Examiner's rejection, and request that it be withdrawn. Applicants submit that the rejected claims (and newly added claims 37-41) are not patentably obvious over Johns et al.

Case Law Concerning Obviousness

When analyzing the issue of obviousness, the differences between the prior art and the claims at issue must be ascertained. [Graham v. John Deer Co., 148 USPQ 459 (Sup. Ct. 1966)]. In connection with the first three "Graham factors," personnel of the U.S. Patent and Trademark Office should: (1) determine the "scope and content of the prior art;" (2) ascertain the "differences between the prior art and the claims at issue;" and (3) determine the "level of ordinary skill in the art." [Official Gazette, 1196 OG 38, March 11, 1997; ADT Corp. v. Lydall, Inc., 159 F.3d 534, 48 USPQ2d 1321 (Fed. Cir. 1998), citing In re Spada, 911 F.2d 705, 15 USPQ 2d 1655 (Fed. Cir. 1990) and Diversitech Corp. v. Century Steps, Inc., 850 F.2d. 1566, 7 USPQ2d 1315 (Fed. Cir. 1988).] With respect to the scope and content of the prior art, each reference must qualify as prior art under 35 U.S.C. §102, and should be in the field of the applicant's endeavor, or be reasonably pertinent to the particular problem with which the inventor was concerned. [*Id.*]

After the above analysis has been performed, the criterion for the determination of obviousness is whether the prior art would have suggested the invention to one of ordinary skill in the art, and that the invention would have a reasonable likelihood of

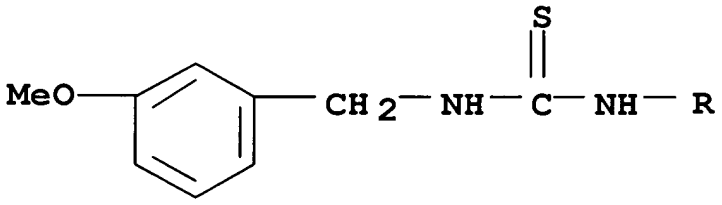
success, viewed in light of the prior art. Both the suggestion and the expectation of success must be founded in the prior art, and not in Applicant's disclosure. [In re Dow Chemical Co., 5 USPQ2d 1529 (Fed. Cir. 1988)].

The mere fact that the prior art can be modified does not make the modification obvious unless the prior art taught or suggested the desirability of the modification. [In re Gordon, 221 USPQ 1125 (Fed. Cir. 1984)]. The prior art must suggest to one of ordinary skill in the art the desirability of the claimed combination. [Fromsom v. Advance Offset Plate, Inc., 225 USPQ 26 (Fed. Cir. 1985).] Good ideas may well appear 'obvious' after they have been disclosed despite having been previously unrecognized. [Arkie Lures, Inc. v. Gene Larew Tackle, Inc., 43 USPQ2d 1294 (Fed. Cir. 1997)].

A reference that teaches away is a significant factor to be considered in determining unobviousness. [In re Gurley, 31 USPQ2d 1130 (Fed.Cir. 1994)].

The Claimed Invention

Rejected claim 1 of the application, as amended hereinabove, describes a compound of the formula:



wherein R is a C_1 - C_{20} linear or branched alkyl, a C_6 - C_7 aryl, a hydroxy-substituted C_6 - C_7 aryl or an alkoxy-substituted C_6 - C_7 aryl, and wherein the compound enhances the oxidative stability of a lipid or oil to which the compound is added, with the proviso that R is not phenyl. Rejected claims 4, 7-9 and 10, and new claims 37-41, of the application are each dependent upon claim 1.

Johns et al.

In contrast with the rejected and new claims of the application, Johns et al. describe (Summary) an examination of the putative anti-aphrodisiac activity of *Tropaeolum tuberosum*, an edible tuber-producing cultigen of the Andes mountains in Peru, in male rats fed a diet containing tubers of this taxon. Johns et al. describe (page 151-152) that pure isothiocyanates and plant extracts were tested for effects on the male and female reproductive processes and for antibiotic activities and nematocial activities (ability to be destructive to soil nematodes, such as roundworms and threadworms). This reference states (page 152) that N,N-di(methoxy-4-benzyl) thiourea was detected in isothiocyanate extracts of tubers of a subspecies of *Tropaeolum tuberosum* named *tuberosum*.

Arguments

First, Applicants respectfully submit that the Johns et al. reference cannot be relied upon by the examiner to support a rejection of Applicants' claims under 35 U.S.C. §103(a). Applicants respectfully submit that the Johns et al. reference is not in the field of the inventors' endeavor, and is not reasonably pertinent to the particular problem with which the inventors were concerned.

In the accompanying Declaration of Thomas P. Abbott (hereinafter "the declaration"), Dr. Abbott states that it is his opinion as an expert in the area of thiourea compounds that, for the reasons that he presents in the declaration, the Johns et al. reference is not in the field of the inventors' endeavor (the use of 1-(3-methoxybenzyl)-3-substituted thiourea compounds for enhancing the oxidative stability of lipid and/or oil compositions), and is not reasonably pertinent to the particular problem with which the inventors were concerned (increasing the oxidative stability of lipid and oil compositions).

Dr. Abbott states in his declaration that, out of the thirteen pages contained in the Johns et al. reference, the only compound discussed therein that has any similarity to the compounds described by claims 1, 4, 7-9 and 10 of the application is the 1,3-di(4-methoxybenzyl)thiourea compound shown and described on page 152 of the reference. He states that this 1,3-di(4-methoxybenzyl)thiourea compound has a different chemical

structure, and different chemical properties, in comparison with 1,3-di(3-methoxybenzyl) thiourea, the compound encompassed within the rejected claims that is the most similar to it.

In addition, Dr. Abbott states in his declaration that the Johns et al. reference does not contain any discussion, teachings or suggestions whatsoever regarding the oxidative stability of lipids and/or oils, let alone the enhancement of the oxidative stability of lipids and/or oils with the use of substituted thiourea compounds. He states that, in contrast with the rejected claims of the application, which describe 1-(3-methoxybenzyl)-3-substituted thiourea compounds that enhance the oxidative stability of lipids or oils to which the compounds are added, the Johns et al. reference describes the testing of pure isothiocyanates and plant extracts of *Tropaeolum tuberosum* for effects on the male and female reproductive processes, and for antibiotic activities and nematocial activities (being destructive to soil nematodes, such as roundworms and threadworms). He states that, for example, the Johns reference makes the following statements about the studies described therein at the locations indicated:

Summary (page 149):

> "The putative anti-aphrodisiac activity of *T. tuberosum* was examined in male rats fed a diet containing tubers of this taxon. Experimental animals and controls showed equal capability in impregnating females, although animals fed *T. tuberosum* showed a 45% drop in their blood levels of testosterone/dihydrotestosterone. This decrease appears to be related to the presence of isothiocyanates in the tubers. Feeding studies of female guinea pigs and *in vitro* studies to test the 17ß-estradiol binding inhibition of plant extracts and of pure isothiocyanates failed to substantiate any estrogenic activity of these taxa. However, preliminary results suggest that N,N-di-(methoxy-4-benzyl)thiourea competitively inhibits estradiol binding and may have estrogenic activity.
>
> The antibiotic, insecticidal, nematocidal and diuretic properties of isothiocyanates substantiate several of the uses of *T. tuberosum* in Andean folk medicine." (Emphasis added.)

Page 150, Second Paragraph:

> "Although magical beliefs accompany these accounts, the use of *T. tuberosum* in affecting human reproductive potential has continued to the present. . . Men refuse to eat these tubers because they believe that to do so produces impotence and an incapacity to have children. . . In modern Bolivia *T. tuberosum* is believed to induce menstruation . . . In folk medicine generally, menstruation is seen as a sign of femininity and fertility . . . and efforts are made using herbs and other means to induce late menstrual periods. . . . Thus the folk uses of *Tropaeolum* spp. as female fertility agents and male antagonists have a certain logic to them." (Emphasis added.)

Dr. Abbott states in his declaration that it is clear from the quotations of the Johns et al. reference set forth above, and from a reading of the remainder of the Johns et al. reference, that the problems that the authors of the Johns et al. reference were attempting to solve are completely different from the problem with which the inventors of the invention described in the rejected claims of the Continuation Application were concerned.

Second, Applicants submit that significant differences exist between the invention described in the rejected claims (and new claims 37-41) and the teachings and suggestions that are present in Johns et al.

In his Declaration, Dr. Abbott states that it is his opinion as an expert in the area of thiourea compounds that, for the reasons that he presents in the declaration, significant differences exist between the teachings and suggestions contained in the Johns et al. reference and the invention described in rejected claims 1, 4, 7-9 and 10 of the patent application.

Dr. Abbott states in his declaration that each of rejected claims 1, 4, 7-9 and 10 of the patent application, as amended in this Preliminary Amendment, contains the phrase, "wherein the compound enhances the oxidative stability of a lipid or oil to which the compound is added." Dr. Abbott states in his declaration that the Johns et al. reference does not contain any discussion, teachings or suggestions whatsoever regarding the oxidative stability of lipids and/or oils, let alone the enhancement of the oxidative stability of lipids and/or oils with the use of substituted thiourea compounds.

Dr. Abbott further states in his declaration that the only compound described by the Johns et al. reference in its thirteen pages that has any similarity to the compounds described in the rejected claims is 1,3-di(4-methoxybenzyl)thiourea. He states that the compound encompassed within the rejected claims that is the most similar to 1,3-di(4-methoxybenzyl)thiourea is 1,3-di(3-methoxybenzyl) thiourea.

Dr. Abbott states in his declaration that 1,3-di(3-methoxybenzyl) thiourea differs from 1,3-di(4-methoxybenzyl)thiourea both structurally, and in its chemical properties.

In his declaration, Dr. Abbott states that 1,3-di(3-methoxybenzyl) thiourea differs from 1,3-di(4-methoxybenzyl)thiourea structurally in that 1,3-di(3-methoxybenzyl) thiourea has the methoxy group present on its two benzene rings in the meta position, whereas 1,3-di(4-methoxybenzyl)thiourea has the methoxy group present on its benzene rings in the para position. He states that this structural difference between these two compounds results in these compounds having different chemical properties. He states that, most significant in connection with the rejected claims of the patent application is that, in comparison with 1,3-di(3-methoxybenzyl) thiourea, 1,3-di(4-methoxybenzyl)-thiourea is significantly less soluble in lipids and oils and, as a result, has a significantly decreased ability to enhance the oxidative stability of a lipid or oil to which it is added.

Dr. Abbott states in his declaration that the less soluble a substituted thiourea compound is in a lipid or oil to which the compound is added, the less the compound will have the ability to enhance the oxidative stability of the lipid or oil (because more of it remains in an undissolved state).

In his declaration, Dr. Abbott describes experiments that he conducted in order to compare the solubility of 1,3-di(4-methoxybenzyl)thiourea and 1,3-di(3-methoxybenzyl) thiourea in refined meadowfoam seed oil. He states that, from these experiments, it can be seen that the solubility of 1,3-di(4-methoxybenzyl) thiourea in refined meadowfoam seed oil is, at most, 25% (one fourth) of the solubility of 1,3-di(3-methoxybenzyl) thiourea in refined meadowfoam seed oil, and is probably less. He states that, as a result, 1,3-di(3-methoxybenzyl) thiourea is three times more effective as an agent to enhance the oxidative stability of a lipid or an oil to which it is added in comparison with 1,3-di(4-methoxybenzyl)thiourea. He further states that, although the results described in the experiments set forth in the declaration concern the solubility of 1,3-di(3-

methoxybenzyl) thiourea and 1,3-di(4-methoxybenzyl)thiourea compounds in refined meadowfoam seed oil, similar results would be expected to occur with other types of lipids and oils.

Further, new compound claims 37-41 do not encompass the compound 1,3-di(3-methoxybenzyl) thiourea.

In view of the discussion presented by Applicants hereinabove, Applicants respectfully disagree with the statement made by the examiner in the office action (page 3) that, ". . . it is common knowledge to those skilled in the art that isomers possess similar chemical and physical properties." The experiments that are set forth in Dr. Abbott's accompanying declaration show that this statement is not true in connection with the compounds 1,3-di(3-methoxybenzyl) thiourea and 1,3-di(4-methoxybenzyl)thiourea. In his declaration, Dr. Abbott shows that the solubility of 1,3-di(4-methoxybenzyl) thiourea in refined meadowfoam seed oil is, at most, 25% (one fourth) of the solubility of 1,3-di(3-methoxybenzyl) thiourea in refined meadowfoam seed oil (and is probably less). Dr. Abbott states that, as a result, 1,3-di(3-methoxybenzyl) thiourea is three times more effective as an agent to enhance the oxidative stability of a lipid or an oil to which it is added in comparison with 1,3-di(4-methoxybenzyl)thiourea.

Third, in contrast with the requirements of the patent case law concerning obviousness, Dr. Abbott states in his declaration that, in his opinion as an expert in the area of thiourea compounds, the Johns et al. reference would not have suggested that the invention described in rejected claims 1, 4, 7-9 and 10 of the application, as amended hereinabove, would have a reasonable likelihood of success. He states that the Johns et al. reference does not contain any discussion, teachings or suggestions whatsoever regarding the oxidative stability of lipids and/or oils, let alone the enhancement of the oxidative stability of lipids and/or oils with the use of substituted thiourea compounds. Further, he states that the only compound described by the Johns et al. reference in its thirteen pages that has any similarity to the compounds described in the rejected claims is 1,3-di(4-methoxybenzyl)thiourea. However, Dr. Abbott has shown via the experiments that are described in his declaration that 1,3-di(4-methoxybenzyl)-thiourea is not very soluble in lipids and oils and, thus, is not effective as an agent to enhance the oxidative stability of a lipid or an oil to which it is added. Thus, Dr. Abbott concludes that the '089

patent would not have suggested that the compounds described by rejected claims 1, 4, 7-9 and 10 of the application would have a reasonable likelihood of success in enhancing the oxidative stability of lipids or oils to which the compounds are added.

2. Rejection of Claims 1, 2 and 5 under 35 U.S.C. §103(a)

In the office action, the Examiner rejected claims 1, 2 and 5 under 35 U.S.C. §103(a) as being unpatentable over Maxwell et al. U.S. Patent No. 3,949,089 ("the '089 patent").

In the office action, the Examiner stated that Applicants claim a compound of the formula given in claim 1 of the present application. Referring Applicants to example 1, specifically column 4, line 28, of the '089 patent, the examiner stated that, "Maxwell et al. teach an isomer of the compound(s), named N-p-methoxybenzyl-N'-methylthiourea (registry number: 30738-98-8) defined by the claims of the present application." The Examiner stated that the difference between the Applicants' claimed invention and what is taught in the Maxwell et al. reference is that the reference's thiourea compound is the positional isomer to that of the presently claimed compound(s). The Examiner further stated that the methoxy substituent on the benzene ring is in the para position, whereas in the presently claimed compound(s) the methoxy substituent is in the meta position. The Examiner stated that it is of common knowledge to those skilled in the art that isomers possess similar chemical and physical properties. The Examiner stated that, thus, it would have been prima facie obvious to one of ordinary skill in the art, in view of the Maxwell et al. reference, to arrive at the presently claimed thiourea compound(s) of the presently claimed formula because Maxwell et al. teach an isomer of the presently claimed compound(s). The Examiner stated that one of ordinary skill in the art would have been motivated, in view of the teachings in the Maxwell et al. reference, to prepare additional antifibrillatory compounds by using the meta- or ortho-isomers of para-hydroxybenzonitrile, as the starting reactants, in the process disclosed by Maxwell et al. in Example 1. The examiner stated that the instantly claimed compounds would therefore have been obvious to one of ordinary skill in the art.

For the reasons presented below, Applicants respectfully traverse the Examiner's rejection, and request that it be withdrawn. Applicants submit that the rejected claims (and newly added claims 37-41) are not patentably obvious the '089 patent.

The '089 Patent (Maxwell et al.)

In contrast with the rejected claims of the application, the '089 patent describes acid addition salts of N-p-methylbenzyl-N',N''-dimethylguanidine and of N-p-methoxybenzyl-N',N''-dimethylguanidine, which are stated to be useful as antifibrillatory agents. The '089 patent also describes methods for treating cardiac arrhythmia with the use of these compounds.

Arguments

First, for the reasons discussed below, Applicants respectfully submit that the '089 patent cannot be relied upon by the Examiner to support a rejection of Applicants' claims under 35 U.S.C. §103(a).

In his Declaration, Dr. Abbott states that, for the reasons presented therein, it is his opinion as an expert in the area of thiourea compounds that the '089 patent is not in the field of the inventors' endeavor (the use of 1-(3-methoxybenzyl)-3-substituted thiourea compounds for enhancing the oxidative stability of lipid and/or oil compositions), and that the '089 patent is not reasonably pertinent to the particular problem with which the inventors were concerned (increasing the oxidative stability of lipid and oil compositions).

Dr. Abbott states in his declaration that the only compound discussed in the '089 patent that has any similarity to the compounds described by claims 1, 2 or 5 of the application is the N-p-methoxybenzyl-N'-methylthiourea compound described in column 4 (EXAMPLE 1). He further states that this N-p-methoxybenzyl-N'-methylthiourea compound, however, is structurally different from the compounds encompassed within claims 1, 2 and 5 of the application. Moreover, Dr. Abbott states that this N-p-methoxybenzyl-N'-methylthiourea compound is being used as an intermediate in the production of a guanidine hydriodide compound, and not as an antioxidant.

Moreover, Dr. Abbott states in his declaration that the '089 patent does not contain any discussion, teachings or suggestions whatsoever regarding the oxidative stability of lipids and/or oils, let alone the enhancement of the oxidative stability of lipids and/or oils with the use of substituted thiourea compounds. He further states that, in contrast with the rejected claims of the application, which describe 1-(3-methoxybenzyl)-3-substituted thiourea compounds that enhance the oxidative stability of lipids or oils to which the compounds are added, the '089 patent describes acid addition salts of N-p-methylbenzyl-N',N"-dimethylguanidine and of N-p-methoxybenzyl-N',N"-dimethylguanidine that are stated to have antiarrhythmic properties, and to be useful as antifibrillatory agents. For example, he states that the '089 patent makes the following statements about the compounds, and utilities thereof, described therein at the locations indicated:

Column 1, Lines 20-32:

> "It has now been found that certain N-benzyl-N',N"-dimethylguanidine acid addition salts, namely the N-p-methylbenzyl- and N-p-methoxybenzyl-N',N"-dimethylguanidine acid addition salts possess unexpected advantages over that drug in the treatment of arrhythmia. These compounds not only have antiarrhythmic properties comparable to bethanidine, but also significantly less sympathetic blocking action, thus making possible the treatment of heart disorders with little or no adverse effect on blood pressure.
>
> Among the types of arrhythmias which the compounds of this invention are effective in suppressing are ventricular fibrillations and atrial fibrillations. It has been found that an effective amount of the compounds, which are most desirably pharmacologically and pharmaceutically acceptable salts according to this invention, may be used to treat and suppress ventricular and atrial fibrillations in mammals, such as humans, dogs, cats and the like."
> (Emphasis added.)

Claim 7:

> "A method of suppressing ventricular or atrial fibrillations in a mammal having a heart disorder which comprises administering to said mammal an effective ventricular or atrial fibrillation suppression amount of a pharmaceutically acceptable acid addition salt of N-p-methoxybenzyl-N'N"-dimethylguanidine." (Emphasis added.)

In his declaration, Dr. Abbott states that it is clear from the above quotations of the '089 patent, and from a reading of the remainder of the '089 patent, that the problems that the inventors of the invention described in the '089 patent were attempting to solve are completely different from the problem with which the inventors of the invention described in the rejected claims of the present patent application were concerned.

Second, in addition to other amendments made to the claim, claim 1 of the application has been amended in the amendments presented hereinabove to add the phrase thereto, "wherein the compound enhances the oxidative stability of a lipid or oil to which the compound is added." Because rejected claims 2 and 5, and new claims 37-41, of the application depend upon claim 1, these claims also contain this limitation. Applicants respectfully submit that the '089 patent clearly would not have suggested Applicants' claimed invention to one of ordinary skill in the art.

In his declaration, Dr. Abbott states that, for the reasons set forth therein, it is also his opinion as an expert in the area of thiourea compounds that significant differences exist between the teachings and suggestions contained in the '089 patent and the invention described in rejected claims 1, 2 and 5 of the patent application, and that one skilled in the art would not look to guanidine compounds for structural guidance in the production of unique thiourea compounds.

In his declaration, Dr. Abbott states that, in contrast with the rejected claims of the application, the '089 patent describes acid addition salts of N-p-methylbenzyl-N',N''-dimethylguanidine and N-p-methoxybenzyl-N',N''-dimethylguanidine, which are stated to be useful as antifibrillatory agents, and methods for treating cardiac arrhythmia with the use of these compounds.

Dr. Abbott states in his declaration that, for the reasons presented therein, in his opinion, the chemical structures of, methods for synthesis, properties and uses of guanidine compounds, which are described in the '089 patent, and thiourea compounds, which are described in the rejected claims of the present application, are unrelated.

In his declaration, Dr. Abbott states that guanidine compounds have a nitrogen atom double bonded to a carbon atom, whereas thiourea compounds have a sulfur atom double bonded to a carbon atom. Further, he states that guanidine compounds have an additional hydrogen substituent, and the thiourea sulfur atom is not hydrogen substituted.

Further, Dr. Abbott states in his declaration that, unlike thiourea compounds, which are not especially basic, or even salt-forming, guanidine compounds are among the most basic of organic compounds. He states that recent publications concerning guanidine compounds are often related to the production of organic super-bases.

Moreover, Dr. Abbott states in his declaration that uses for guanidine compounds, and/or derivatives or salts thereof, include rubber-curing acceleration and use as antifibrillatory agents for the treatment of cardiac arrhythmia. In contrast, he states that thiourea compounds, and their organic derivatives and salts, are used as antioxidant agents, and for the recovering of metal.

In his declaration, Dr. Abbott states that, in the organic chemistry textbook An Introduction to Organic Chemistry, A. Lowy and B. Harrow (Wiley and Sons, NY, NY (1961)), which was written on the basis of related compound structures, guanidine compounds are located in the chapter describing acid amides, whereas thiourea compounds are located in the chapter describing organosulfur compounds. A copy of the front cover of this textbook, as well as copies of pages 130-131 and 138-139 thereof (from chapter 11), which show the structure, and describe the properties, of guanidine in connection with a discussion of acid amides, and copies of pages 214-215 and 218-219 thereof (from chapter 18), which show the structure of thiourea, and describes it as being the sulfur analog of urea, in connection with a discussion of organosulfur compounds, are enclosed herewith for the examiner's review.

In his declaration, Dr. Abbott states that, in a different organic chemistry textbook, Organic Chemistry, R.Q. Brewster and W. E. McEwen (Prentice-Hall, (1961)), guanidine compounds are described in the chapter describing carbonic acid derivatives,

whereas thiourea compounds are described in the chapter describing aliphatic sulfur compounds. The front cover of this textbook, as well as a copy of page 260 thereof (from chapter 13), which shows the structure of guanidine in connection with a discussion of derivatives of carbonic acid, and page 318 thereof (from chapter 15), which contains a subsection on thioureas in connection with a discussion of aliphatic sulfur compounds, are enclosed herewith for the examiner's review.

In his declaration, Dr. Abbott states that many modern organic chemistry textbooks, such as Advanced Organic Synthesis, M.B. Smith and J. March (Wiley-Interscience, NY, NY. 5th ed. (2001)), do not group compounds by related properties, but rather by compound synthesis methods or mechanisms of synthesis. He further states that substituted thiourea compounds and guanidine compounds are not produced by the same methods. Thus, he states, these two groups of compounds are generally located in different sections in connection with different methods of synthesis in these types of organic chemistry textbooks. A copy of the front cover of Advanced Organic Synthesis, as well as copies of pages 1190-1193 thereof, showing that substituted thiourea compounds and guanidine compounds are located in different sections of this textbook, are enclosed herewith for the examiner's review.

In his declaration, Dr. Abbott states that he performed computer searches for publications describing guanidine compounds and thiourea compounds in the same article using: (a) the ArticlesFirst database of journal articles; (b) the WorldCat database of books; and (c) the Medline database of scientific publications. He states that the ArticlesFirst database provided one reference in which both thiourea and guanidine were listed as reducing agents. He states that the Medline database provided 2367 references for guanidine compounds, 2978 references for thiourea compounds, and no references describing thiourea compounds and guanidine compounds in the same article. He states that the WorldCat database found hundreds of references for each class of compound separately, but only one publication (a thesis paper) describing the two classes of compounds together ("Investigation of Ammoniation and Ammonolysis Reactions by Pressure-composition Isotherms," W.R.M. Bride. Thesis, Austin, TX. 1955).

In view of the above, Dr. Abbott states in his declaration that it is clear that the structure of a substituted guanidine compound effective for controlling cardiac

arrhythmia does not suggest a substituted thiourea compound effective for enhancing the oxidative stability of oil or lipid compositions to those of skill in the art. He states that a substituted guanidine compound does not imply that a similarly substituted thiourea compound would have similar or related properties, uses or methods for synthesis. He further states that those of skill in the art would not look to substituted guanidine compounds for guidance regarding the properties of substituted thiourea compounds.

In his declaration, Dr. Abbott states that the only compound described by the '089 patent that has any similarity to the compounds described in the rejected claims is N-p-methoxybenzyl-N'-methylthiourea. He states that the compound encompassed within the rejected claims that is the most similar to N-p-methoxybenzyl-N'-methylthiourea is 1-(3-methoxybenzyl)-3-methyl-2-thiourea. He further states that 1-(3-methoxybenzyl)-3-methyl-2-thiourea differs from N-p-methoxybenzyl-N'-methylthiourea structurally, and likely in its chemical properties.

In his declaration, Dr. Abbott states that 1-(3-methoxybenzyl)-3-methyl-2-thiourea differs from N-p-methoxybenzyl-N'-methylthiourea structurally in that the methoxybenzyl group present on the benzene ring is in the meta position, whereas N-p-methoxybenzyl-N'-methylthiourea has the methoxy group present on its benzene ring in the para position. He states that, based upon the experiments that are presented in Section 10 of the declaration, which involve a similar set of circumstances, he would predict that the structural difference between these two compounds would result in these compounds having different chemical properties. He states that, based upon these experiments, he would predict that N-p-methoxybenzyl-N'-methylthiourea, in comparison with 1-(3-methoxybenzyl)-3-methyl-2-thiourea, would be significantly less soluble in lipids and oils and, as a result, have a significantly decreased ability to enhance the oxidative stability of a lipid or oil to which the compound is added. He states that, in the '089 patent, the N-p-methoxybenzyl-N'-methylthiourea compound is being used as an intermediate in the production of a guanidine hydriodide compound, and not as an antioxidant.

Further, new compound claims 37-41 do not include a compound wherein the R variable is defined as being methyl.

In view of the discussion presented by Applicants hereinabove, and in view of the statements made by Dr. Abbott in his declaration, Applicants respectfully disagree with the statement made by the examiner in the office action (page 4) that, ". . . it is common knowledge to those skilled in the art that isomers possess similar chemical and physical properties." Applicants respectfully submit that the experiments that are set forth in Dr. Abbott's declaration show that this statement is not true in connection with the compounds 1,3-di(3-methoxybenzyl) thiourea and 1,3-di(4-methoxybenzyl)thiourea. In his declaration, Dr. Abbott shows that the solubility of 1,3-di(4-methoxybenzyl) thiourea in refined meadowfoam seed oil is, at most, 25% (one fourth) of the solubility of 1,3-di(3-methoxybenzyl) thiourea in refined meadowfoam seed oil (and is probably less). Dr. Abbott states in his declaration that, as a result, 1,3-di(3-methoxybenzyl) thiourea is three times more effective as an agent to enhance the oxidative stability of a lipid or an oil to which it is added in comparison with 1,3-di(4-methoxybenzyl)thiourea.

Third, in contrast with the requirements of the patent case law concerning obviousness, Dr. Abbott states in his declaration that, for the reasons presented therein, it is also his opinion as an expert in the area of thiourea compounds that the '089 patent would not have suggested that the invention described in rejected claims 1, 2 and 5 of the application, as amended in this Preliminary Amendment, would have a reasonable likelihood of success. Dr. Abbott states that, as is discussed in his declaration, the '089 patent does not contain any discussion, teachings or suggestions whatsoever regarding the oxidative stability of lipids and/or oils, let alone the enhancement of the oxidative stability of lipids and/or oils with the use of substituted thiourea compounds. Further, Dr. Abbott states that the N-p-methoxybenzyl-N'-methylthiourea compound described in line 28, column 4, of the '089 patent is used only as an intermediate during the synthesis of a guanidine hydriodide compound (the final product described in Example 1 of the '089 patent). Thus, Dr. Abbott states that the '089 patent would not have suggested that the compounds described by rejected claims 1, 2 and 5 of the application would have a reasonable likelihood of success in enhancing the oxidative stability of lipids or oils to which the compounds are added.

Fourth, Applicants respectfully submit that the '089 patent teaches away from the invention described in rejected claims 1, 2 and 5 of the application. The '089 patent

teaches that the activity of the salts described therein resides in the cation. For example, the '089 patent makes the following statements at column 1, lines 55-68, and column 2, lines 1-4:

> "The activity of the acid addition salts of N-p-methylbenzyl-N',N''-dimethylguanidine and of N-p-methoxybenzyl-N',N''-dimethylguanidine resides in the cation, the nature of the anion only being important for administration requirements. . . Salts which are especially preferred for therapeutic use are the chlorides, sulphates and sulphonates such as the p-toluenesulphonate. The salts of N-p-methoxybenzyl-N',N''-dimethylguanidine are particularly preferred from the point of view of their therapeutic activity." (Emphasis added.)

In contrast with the teachings and suggestions of the '089 patent, the activity of the compounds described in the present application (enhancing the oxidative stability of a lipid or oil to which the compound is added), which is quite different from the activity discussed in the '089 patent for the compounds described therein (activity as antifibrillatory agents in a mammal having a heart disorder), does not reside in a cation.

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In view of the discussion presented above, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 1, 2, 4, 5 and 7-10 of the application, and to allow claims 1-2, 4-5 and 7-41, and pass the application to issue.

If, after considering this Preliminary Amendment, the Examiner believes that any issues still remain in the prosecution of the application, the Examiner is requested to telephone Applicants' attorney at the telephone number set forth hereinbelow to discuss the same.

Respectfully submitted,

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